PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 025-ST-02-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IT 03/00820	International filing date *(day/month/year)* 16.12.2003	Priority date *(day/month/year)* 19.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/19		
Applicant SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.p.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.06.2004	07.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Beranová, P Telephone No. +49 30 25901-333

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT 03/00820

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-64 as originally filed

Claims, Numbers

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-6,8,9,13,14
	No:	Claims	1-3,7,10-12,15
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 Reference is made to the following documents:

D1: WINEGAR D A ET AL: "Role of peroxisome proliferator-activated receptors in atherosclerosis" CURRENT OPINION IN CARDIOVASCULAR, PULMONARY AND RENAL INVESTIGATIONAL DRUGS 2000 UNITED KINGDOM, vol. 2, no. 3, 2000, pages 233-243, XP008029337 ISSN: 1464-8482

D2: BROOKS D A ET AL: "Design and synthesis of 2-methyl-2-{4-[2-(5-methyl-2-aryloxazol-4-yl)ethoxy]phenoxy}propionic acids: a new class of dual PPARalpha/gamma agonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 13, 21 June 2001 (2001-06-21), pages 2061-2064, XP002184099 ISSN: 0022-2623

D3: LALEZARI I ET AL: "LR-16 A COMPOUND WITH POTENT EFFECTS ON THE OXYGEN AFFINITY OF HEMOGLOBIN ON BLOOD CHOLESTEROL AND ON LOW DENSITY LIPOPROTEIN" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 85, no. 16, 1988, pages 6117-6121, XP001161155 1988 ISSN: 0027-8424

D4: GB-A-1 422 679 (FUNAI PHARMACEUTICAL IND LTD) 28 January 1976 (1976-01-28)

D5: GRONOWITZ S ET AL: "POTENTIAL HYPOLIPIDEMIC AGENTS XIX. SYNTHESIS AND LIPID-LOWERING PROPERTIES OF THIOPHENE DERIVATIVES RELATED TO CLOFIBRATE" ACTA PHARMACEUTICA SUECICA, XX, XX, vol. 15, no. 5, 1978, pages 361-367, XP001053343 ISSN: 0001-6675

5.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 3, 7, 10 - 12 and 15 is not new in the sense of Article 33(2) PCT.

The document **D2** discloses propionic acid derivatives which are PPARα/γ agonists. The paper reports that compound No. 8 which falls under the presently claimed formula (I) (R = Phe and both R_1 and R_2 are methyl) is a glucose-lowering agent, elevates HDL and reduces serum triglyceride levels (page 2063, right-hand column, 1st and 2nd paragraphs; Chart 1; Table 1). This document is thus considered to be relevant for novelty of the subject-matter of claims 1 - 3, 7, 10 - 12 and 15.

D3 shows that oral administration of LR-16 to rats fed with cholesterol-rich diet reduces serum cholesterol and LDL cholesterol with HDL cholesterol unchanged wherein the compound LR-16 falls under formula (I) (page 6117, abstract; Scheme 1). D3 is therefore novelty-destroying for claims 1, 2, 10 - 12 and 15.

D5discloses hypolipidemic agents, namely compounds Nos. 1 - 3 having the same chemical structure as the presently claimed compounds (Table 1; page 364, 1st paragraph). This document is therefore relevant for novelty of claims 1, 3, 10 - 12 and 15.

5.3 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 - 15 does not involve an inventive step in the sense of Article 33(3) PCT.

The document **D1** is regarded as being the closest prior art and discloses PPARγ agonists, such as fenofibrate, which lower serum triglycerides and LDL cholesterol, increase HDL cholesterol and improve insulin resistance and reports the role of PPARγ agonists in stroke and atherosclerosis (Table 1; page 236, left-hand column, 5th paragraph; page 236, right-hand column, 2nd paragraph).

. The present application therefore differs from this known D1 in that the substituent "**Q**" is the group **-CO-** in fenofibrate (D1) (while in the present claim 1 it is selected from NH, O, S, -NHC(O)O-, -NHC(O)NH-, -NHC(O)S-, -OC(O)NH-, -NHC(S)O-, **-C(O)NH-**).

The problem to be solved by the present invention may therefore be regarded as provision of further compounds with the same pharmacological activity, i.e. triglycerides and cholesterol lowering effect.

The solution proposed in the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: according to the concept of bioisosterism, the groups -CO- and -C(O)NH- are considered as being equivalent. Compounds which include such bioisosteric substituents can therefore be expected to possess the same pharmacological activity. The skilled person would therefore regard the replacement of the group **-CO-** (known from D1) by **-C(O)NH-** (as in the present application) as an obvious option to solve the problem posed.

A similar reasoning as above is also valid with regard to the document **D5** in which the substituent "Y" (corresponding to "Q" of the presently claimed formula (I)) is selected from **-CH_2-**, -CH_2O-, -CH_2CH_2- and **-CH=CH-** (claim 1; page 1, lines 20 - 26).

The substituent **-CH_2-** (known from D5) can thus be replaced by the presently claimed substituents **-NH-** and **-O-** because these groups are considered as bioisosteres. In the case of **-CH=CH-** (D5), it can be replaced by the presently claimed (bioisosteres) **-CONH-**

or **-NHCO-** without exercising inventive step.

It is therefore submitted that a part of claims 1 - 15 lacks inventive step in the sense of Article 33(3) PCT.

5.4 Furthermore, it is noted that the terms "**aryl**", "**heteroaryl**", "**alkyl**" and "**alkoxy**" (claims 1 - 3) meet clarity requirements of Article 6 PCT. However, these terms are objected for lack of support and disclosure, the objection being that the applicant, whilst claiming all ways of achieving the result has provided support and disclosure within the meaning of Article 5 and 6 PCT for only a small number of ways. Such claims are not supported over their whole breadth, and are not disclosed over their whole breath.

5.5 The use of the expressions "**particularly**", "**such as**" and "**e.g.**" in claims 7, 9 and 11 renders the subject-matter of these claims unclear since it introduces an ambiguity in the claims. It is stressed that these expressions have no limiting effect on the scope of the claims. The features following such expressions are to be regarded as entirely optional.